Serum Uric Acid is Associated With New-Onset Diabetes in Hypertensive Patients With Left Ventricular Hypertrophy: The LIFE Study

Benedicte P. Wiik[a], Anne C.K. Larstorp, MD[a], Aud Høieggen, MD, PhD[a], Sverre E. Kjeldsen, MD, PhD[a,b], Michael Hecht Olsen, MD, PhD[c], Hans Ibsen, MD[d], Lars Lindholm, MD, PhD[e], Björn Dahlöf, MD, PhD[f], Richard B. Devereux, MD[g], Peter M. Okin, MD[g], Kristian Wachtell, MD, PhD[h].

From [a]Departments of Cardiology and Nephrology, Oslo University Hospital, Ullevaal, Oslo, Norway; [b]Department of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA; [c]The Cardiovascular Research Unit, Cardiology Section, Department of Internal Medicine, Glostrup University Hospital, Glostrup, Denmark; [d]Division of Cardiology, Holbaek Hospital, Holbaek, Denmark; [e]Umeå University Hospital, Umeå, Sweden; [f]Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden; [g]Greenberg Division of Cardiology, Weill Cornell Medical College, New York City, USA; [h]The Heart Center, Rigshospitalet, Copenhagen, Denmark.

Abstract

Objective: It is unclear whether serum uric acid (SUA) is associated with development of new-onset diabetes (NOD) in patients with hypertension and left ventricular hypertrophy (LVH). The aim of the present investigation was to test the hypothesis that SUA predicts development of NOD in these patients.

Design and method: In the LIFE study, a double masked, parallel-group design, 9193 patients with hypertension and electrocardiographic (ECG) LVH were randomized to losartan- or atenolol-based antihypertensive treatment and followed for a mean of 4.9 years. At baseline, 7489 patients with available SUA measurements did not have diabetes mellitus and were thus at risk of its development during the study. We used Cox regression analyses to investigate whether SUA predicted development of NOD.

Results: NOD developed in 522 of 7489 patients. The association between baseline SUA and development of NOD was significant (HR 1.29 per SD [1.3 mg/dl], 95% CI 1.18-1.42, $P < 0.001$) after adjustment for treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, estimated glomerular filtration rate and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage. In parallel analyses, baseline quartiles of SUA were significantly associated with increasing NOD (HR 1.28, 95% CI 1.18-1.40, $P < 0.001$). Time-varying SUA was also associated with NOD (HR 1.10 per SD [1.3 mg/dl], 95% CI 1.02-1.19, $P = 0.015$).

Conclusion: Our analysis suggests that serum uric acid is an independent risk marker for new-onset diabetes in hypertensive patients with left ventricular hypertrophy.

Key words: New-onset diabetes, serum uric acid, hypertension, left ventricular hypertrophy

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated the superiority of a losartan-based regimen over atenolol-based regimen for reduction of cardiovascular (CV) morbidity and mortality. The primary endpoint was a composite of cardiovascular death, myocardial infarction, and stroke. New-onset diabetes (NOD) was a pre-specified secondary endpoint.[1]

In LIFE patients NOD could be predicted by a risk score using significant variables from multivariate analyses, including serum glucose concentration, body mass index (BMI), serum HDL cholesterol concentration, systolic blood pressure (SBP) and prior use of antihypertensive drugs. Univariate analyses also showed a relation between serum uric acid (SUA) and risk of new-onset diabetes.[2] In the same population baseline SUA was significantly associated with increased rate of the composite outcome of CV death, nonfatal myocardial infarction, or nonfatal stroke, especially in women,[3,4] and with new-onset atrial fibrillation.[5] SUA increased most in the group receiving atenolol. Losartan competes with the reabsorption of uric acid in the tubules and thereby leads to increased uric acid excretion by the kidneys, which may explain this difference.[3]

The association of hyperuricemia with hyperglycemia was first described by Kylin.[6] In recent years the association of SUA with diabetes has been studied in different ethnic groups. According to these studies, it is not settled to what extent SUA independently predicts the development of diabetes.[7] Whereas it was suggested that SUA is an independent risk factor for diabetes in the Rotterdam study, a cohort study of 4536 healthy subjects free from diabetes at baseline, aged 55 years and older,[8-10] it has previously not been investigated whether SUA is associated with the development of NOD in patients with hypertension and left ventricular hypertrophy (LVH), a population with particular high risk of developing diabetes[2] and in which SUA predicts major cardiovascular disease.[3] Thus, the aim of the present investigation

was to test our hypothesis[2] that SUA predicts development of NOD in hypertensive patients with LVH.

Methods

Participants: The LIFE study population consists of 9193 patients aged 55 to 80 with previously untreated or treated essential hypertension and ECG-LVH, by Cornell voltage-duration product or Sokolow-Lyon voltage.[11] The LIFE study included patients with mean trough sitting diastolic BP of 95-115 mmHg and/or a mean sitting systolic BP of 160-200 mmHg after 1-2 weeks on single-blind placebo treatment, who had not suffered a myocardial infarction or stroke within 6 months, and did not have known LV ejection fraction < 40%, or required treatment with a β-blocker, angiotensin converting enzyme-(ACE)-inhibitor, or angiotensin receptor-(AT_1)-antagonist. The mean age at inclusion was 66.9 years, 54.1% were women, and the mean baseline BP was 174.4/97.8 mmHg.[1]

Of the 9193 patients participating in the LIFE study, 1195 patients with diabetes mellitus at study baseline were excluded from the current analysis, leaving 7998 patients who were at risk of developing diabetes to be included in the present study. However, 509 patients did not have their SUA measured at baseline. These patients were excluded, leaving 7489 to be included in the statistical analyses. They were quite similar to the rather few patients who did not have SUA at baseline except for small differences in baseline DBP (98.0 vs. 98.9 mmHg, P = 0.02) and ISH status (13.8 vs. 10.2 %, P = 0.02).

If a patient who did not have diabetes at baseline had a non-fasting serum glucose concentration of 144 mg/dl or more, further investigations were made (including repeated fasting glucose or an oral glucose tolerance test, or both).[2] New-onset diabetes mellitus was defined in the LIFE study according to the 1985 World Health Organization (WHO) criteria.[2] Once diabetes was determined to be present on the basis of this definition, the investigator

entered the information into the database. New recommendations for diagnosing NIDDM, mainly using fasting glucose of 126 mg/dl or more, were published by WHO in 1999 while the study was still in progress.[2] Study protocol was not changed, and 1999 criteria was not advocated, but it was decided before the end of the study that all patients who were diagnosed with diabetes during the study would be included in the analyses regardless of the criteria (WHO 1985 or WHO 1999) upon which the diagnosis was based. The patients were followed for a mean of 4.9±0.8 years.

Procedures: The LIFE study was a double-masked, randomized, parallel-group trial. The primary objective was to evaluate the long-term effects of losartan- compared with atenolol-based antihypertensive therapy in patients with hypertension and ECG-LVH on the incidence of cardiovascular morbidity and mortality.[1] The LIFE study design, organization, clinical measures, endpoint definitions, basis for choice of comparative agents, statistical power calculations, recruitment details, baseline characteristics, 1-year follow-up, and primary results have been published.[1,12-13]

The primary endpoint was a composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction. Other pre-specified outcome measures were components of the primary composite endpoint, total mortality, hospitalization for angina pectoris, hospitalization for heart failure, coronary or peripheral revascularization procedures, resuscitated cardiac arrest, and new-onset diabetes mellitus.[1]

The trial protocol was approved by local ethics committees and performed in accordance with the Declaration of Helsinki. All participants gave their informed consent. The study was overseen by an independent data and safety monitoring board.

Routine laboratory tests were performed in 2 central laboratories, with validation of comparable results using split samples. The study ran its full course and endpoint follow-up was stopped on September 16, 2001.[1]

Statistical methods: All endpoints were analyzed using the intention-to-treat approach. Participants who experienced > 1 endpoint were counted as having an event in all relevant endpoint analyses; however, only the first event in a specific category was counted in individual analyses.[2]

Baseline clinical, demographic and laboratory data were assessed for association with new-onset diabetes. Estimated Glomerular Filtration Rate (eGFR) was calculated using the MDRD formula ($175 \times [(\text{s-creat}/88.4)^{-1.154}] \times \text{age}^{-0.203} \times$ gender constant (men: 1.00; women: 0.742) and included as covariate in all multivariate models.

Univariate Cox proportional hazard regression models were used to examine the association between SUA and other possible risk factors and the risk of new-onset diabetes, presented as relative risk (i.e. the hazard ratio [HR]) and its 95 % confidence interval (CI). Variables that had a significant univariate effect or were considered as clinically relevant were maintained when multivariate models were developed. Impact of SUA was calculated in a main multivariate model adjusting for study treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage. We developed additional multivariate models, using the main multivariate model mentioned above and also adjusting for concomitant treatment with hydrochlorothiazide, baseline BMI and baseline HDL. When plausible, interaction analyses were performed using Cox proportional hazard models with SUA entered as time-varying covariate, a possible effect modifier entered as standard covariate and a multiplicative interaction product of time-varying SUA and the possible effect modifier entered as standard covariate. All the included time-varying variables were corrected for missing values: If a value was missing during follow-up, it was replaced by the previous value. These models were used to analyze baseline SUA, baseline quartiles of SUA, and time-

varying SUA as predictors of NOD, computed per 1 SD (1.3 mg/dl) of mean baseline SUA for the continuous variables. The same models were also used to compare the highest quartile of SUA with the three lowest quartiles at baseline, and after 1, 2, 3 and 4 years in regards to risk of developing NOD. A two tailed $P < 0.05$ was required for statistical significance.

Results

Mean baseline SUA was 5.54±1.3 mg/dl, with a range of 1.16-11.93 mg/dl in the 7489 patients included in the analysis. SUA values were normally distributed at baseline and after 1, 2, 3 and 4 years. Average increase of SUA from baseline to study end was 0.74±1.3 mg/dl, also normally distributed.

Demographic and clinical characteristics of the patients in relationship to baseline quartiles of SUA are compared in Table 1. There were significant differences between the quartiles of baseline SUA in age, gender, race, weight, height, BMI, diastolic blood pressure, pulse pressure, heart rate, hemoglobin, serum sodium, potassium, creatinine, eGFR, urinary albumin/creatinine ratio, total and HDL cholesterol, glucose, history of stroke, history of ischemic heart disease, alcohol and Framingham risk score. The groups were similar with respect to systolic blood pressure, Sokolow-Lyon voltage, Cornell voltage-duration product, smoking, physical exercise habits, TIA, peripheral vascular disease and chronic obstructive pulmonary disorder (COPD).

During a mean follow-up of 4.9±0.8 years, new-onset diabetes mellitus developed in 522 patients (7%). There was a higher incidence of diabetes in higher quartiles of baseline SUA. The incidence of NOD rose from about 3% in the 1st quartile of SUA at baseline to approximately 7% in the 2nd and 3rd quartiles of baseline SUA to nearly 11% in the 4th quartile of baseline SUA (Figure 1).

The statistically significant univariate predictors of NOD were baseline and time-varying SUA, BMI, baseline Cornell product, creatinine, eGFR, Framingham risk score, glucose, exercise, HDL, heart rate, hemoglobin, potassium, pulse pressure, systolic blood pressure, total cholesterol, treatment (atenolol vs. losartan), weight, maximal dose of hydrochlorothiazide during study, time-varying Sokolow-Lyon and Cornell product, and time-varying diastolic blood pressure (Supplemental Table).

The relation of SUA to the development of new-onset diabetes is examined further in Table 2. In the main multivariate model, after adjustment for treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage, HR was 1.29 per SD (1.3 mg/dl) increase in baseline SUA, 95% CI 1.18-1.42, $P < 0.001$. In parallel analyses, baseline quartiles of SUA were significantly associated with NOD (HR 1.28, 95% CI 1.18-1.40, $P < 0.001$) and time-varying (change from baseline) SUA was also associated with NOD (HR 1.10 per SD [1.3 mg/dl] increase, 95% CI 1.02-1.19, $P = 0.015$).

In additional models using the main multivariate model and also adjusting for concomitant treatment with hydrochlorothiazide and/or baseline BMI and/or baseline HDL, the association of baseline SUA and baseline quartiles of SUA with NOD was still highly significant (Table 2). When using the main multivariate model and also adjusting for concomitant treatment with hydrochlorothiazide, the association between time-varying SUA and NOD was no longer significant (HR 1.07, 95% CI 1.00-1.16, $P = 0.066$). Similarly, when using the main multivariate model and also adjusting for baseline HDL and BMI, the association between time-varying SUA and NOD was not significant (HR 1.03, 95% CI 0.95-1.11, $P = 0.50$). As a consequence hereof we analyzed potential interactions with time-varying SUA and NOD; study treatment (HR 0.91, 95% CI 0.79-1.04, $P = 0.18$), maximal dose of

hydrochlorothiazide (HR 0.99, 95% CI 0.99-1.00, P = 0.04), HDL (HR 1.39, 95% CI 1.14-1.70, P = 0.001) and BMI (HR 1.00, 95% CI 0.99-1.01, P = 0.40).

Our analyses showed an increasing risk of developing NOD with higher baseline quartile of SUA. The results compared to quartile 1, were HR 2.30, 95% CI 1.69-3.13, P < 0.001 for quartile 2, HR 2.38, 95% CI 1.75-3.25, P < 0.001 for quartile 3, and HR 3.65, 95% CI 2.73-4.89 for quartile 4. These results were unaltered when adjusting for treatment.

In univariate Cox analyses, the risk of NOD in the highest quartile of SUA compared to the lowest three quartiles was HR 1.94, 95% CI 1.62-2.31, P < 0.001 at baseline, HR 2.26, 95% CI 1.87-2.73, P < 0.001 at year 1, HR 1.73, 95% CI 1.37-2.19, P < 0.001 at year 2, HR 2.02, 95% CI 1.52-2.69, P < 0.001 at year 3, and HR 1.87, 95% CI 1.27-2.75, P = 0.001 at year 4 (Figure 2).

In the main multivariate model adjusting for study treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage, the risk of NOD in the highest quartile of SUA compared to the lowest three quartiles was HR 1.48, 95% CI 1.22-1.80, P < 0.001 at baseline, HR 1.91, 95% CI 1.55-2.34, P < 0.001 at year 1, HR 1.44, 95% CI 1.12-1.86, P = 0.004 at year 2, HR 1.70, 95% CI 1.25-2.31, P = 0.001 at year 3, and HR 1.53, 95% CI 1.02-2.31, P = 0.04 at year 4.

After adjusting for study treatment, concomitant treatment with hydrochlorothiazide, baseline BMI, HDL, serum glucose, eGFR, urinary albumin/creatinine ratio and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage, the risk of NOD in the highest quartile of SUA compared to the lowest three quartiles was HR 1.27, 95% CI 1.05-1.55, P = 0.015 at baseline, HR 1.55, 95% CI 1.25-1.91, P < 0.001 at year 1, HR 1.16, 95% CI 0.89-

1.50, P = 0.27 at year 2, HR 1.37, 95% CI 1.00-1.86, P = 0.05 at year 3, and HR 1.28, 95% CI 0.85-1.93, P = 0.24 at year 4.

Discussion

The present investigation demonstrates that SUA is associated with NOD in hypertensive patients with LVH, independent of other predictors of diabetes in the LIFE study. The associations were strong, both with regards to SUA levels at baseline, time-varying SUA, and SUA quartiles at baseline and quartiles at 1, 2, 3 and 4 years after baseline. Our findings in hypertensive patients with LVH are in agreement with findings in other populations.[6-10]

Relationship of diabetes to SUA levels

In our analyses we considered baseline SUA, baseline quartiles of SUA and time-varying SUA as predictors of NOD. We also compared the lowest quartile of baseline SUA with each of the others. Finally the highest quartile of SUA was compared to the three lowest quartiles at baseline and after 1, 2, 3 and 4 years, with respect to risk of NOD. In all these analyses, the results were clearly significant. Furthermore, a strength of our findings is that adjusting the analysis for study treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage did not influence the statistical significance of the association of SUA with NOD.

Using an additional model adjusting for study treatment and hydrochlorothiazide, baseline BMI, HDL, serum glucose, eGFR, urinary albumin/creatinine ratio and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage, the associations were generally

weaker but still significant, except for the analyses of time-varying SUA as a predictor of NOD, and comparing the highest quartile of SUA with the rest of the population 2, 3 and 4 years after baseline in regards to risk of NOD. The additional model included BMI and HDL, which are well known risk factors of new-onset diabetes, usually emphasized more strongly than SUA.[2] Our results suggest that even if there is a strong association between SUA and NOD, BMI and HDL and also baseline glucose (which was adjusted for in all models) are more important predictors, and become still more important over time.

The ability of time-varying SUA in predicting diabetes was weaker than baseline SUA and influenced particularly by concomitant treatment with hydrochlorothiazide and by HDL cholesterol. This finding with hydrochlorothiazide may represent the well known strong association of diuretic use with new onset diabetes. The much stronger ability of HDL cholesterol to interact with the time-varying SUA and new diabetes relationship may however suggest an interesting biological pathway and give insight into the mechanism of how SUA manifests its impacts on new diabetes. Interaction with randomized treatment was however not significant arguing against benefits of losartan on preventing new diabetes (2) was through the SUA effects (3).

The reference range of SUA is between 2.0 and 7.0 mg/dl for men, and between 2.0 and 6.0 mg/dl for women.[14] The total population of this study had a mean value of 5.5 mg/dl at baseline, which is high normal. At year 4 the mean value was 6.1 mg/dl. The patients in the upper quartile of baseline SUA are hyperuremic on average, with mean value of 7.3 mg/dl, ranging from 6.4 to 11.9 mg/dl.

The analyses show an increasing association from baseline to year 1, and from year 2 to year 3. The association decreased from year 1 to year 2 and from year 3 to year 4 (Figure 2). This is most likely due to random variation. As the power analyses of the LIFE study was based on the composite cardiovascular endpoint, and not on the endpoint of NOD, such

variations may appear due to limited statistical power when analyzed from one year to the next.

High SUA as a risk factor for diabetes has been a matter of discussion. Hyperuricemia has been considered to be a result of insulin resistance rather than its precursor.[9] A number of studies have reported significant associations between SUA levels and individual components of the metabolic syndrome, which increase the risk of atherosclerotic cardiovascular disease and type 2 diabetes. A study by Hyon et al indicated that the prevalence of the metabolic syndrome increased substantially with increasing levels of serum uric acid.[15] A study in rats showed that fructose-induced hyperuricemia plays a pathogenic role in the metabolic syndrome, and it has been shown that SUA is associated with oxidative stress and production of tumor necrosis factor-α, which are both related to the development of diabetes.[9]

Moreover, it has been shown that uric acid increases insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake.[16] Uric acid may also contribute to the risk of diabetes mellitus by a direct cytotoxic effect on the pancreatic B-cells via its alloxan-like derivatives.[17] In our study we observed that uric acid could be related to the development of diabetes, and the above mentioned findings support high SUA as a possible risk factor of type 2 diabetes.

Limitations

The LIFE study population was of older age and mainly white ethnicity. Participants were derived from a high-risk population of hypertensive patients and the outcome should be interpreted in this context. The adoption of a 1999 WHO recommendation for diagnosing type 2 diabetes during the later part of the LIFE study, led the Steering Committee to accept patients with diabetes diagnosed according to either the 1999 and 1985 recommendations.[2]

Conclusion

Serum uric acid is independently associated with new-onset diabetes in hypertensive patients with LVH. There are several factors which are significantly associated with development of new-onset diabetes in hypertensive patients with LVH.[2] Some factors are well-known, like obesity, high serum glucose concentration and low HDL cholesterol values. These are probably more important predictors for NOD than SUA, and well-established targets for therapeutic intervention in order to prevent development of diabetes. However, our current findings have potentially important clinical implications. Further investigation with uric acid lowering drugs (e.g. allopurinol) may evaluate if serum uric acid may be an independent target for therapeutic intervention in hypertensive patients with ECG-LVH to prevent the development of new-onset diabetes mellitus.

Disclosure The LIFE study was sponsored by Merck & Co., Inc., Whitehouse Station, New Jersey. The data base is in the possession of the investigators (the authors of this paper) who have also done all statistical work. Authors Aud Høieggen, Sverre E. Kjeldsen, Michael Hecht Olsen, Hans Ibsen, Lars Lindholm, Björn Dahlöf, Richard B. Devereux, Peter M. Okin, and Kristian Wachtell have received lecture honoraria from Merck & co. and other pharmaceutical companies.

References

1. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002;359:995-1003.
2. Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman JM, Snapinn S. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *Journal of Hypertension* 2002;20:1879-1886.
3. Høieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, de Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, Chen C, Dahöf B. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney International* 2004;65:1041-1049.
4. Kizer JR, Hoieggen A, Alderman MH, Kjeldsen S, Dahlöf B, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm L, Nieminen M, Omvik P, Oparil S, Wedel H, Wachtell K, Snapinn S, Edelman J, Devereux R. Serum uric acid and ischemic stroke risk among hypertensive patients with left ventricular hypertrophy: The LIFE Study. *J Am Coll Cardiol* 2004; 43:475A.
5. Zacks E, Wachtell K, Gerdts E, Dahlöf B, Ibsen H, Julius S, Kjeldsen SE, Devereux RB. Associaion of uric acid level with new-onset atrial fibrillation in treated hypertensive patients: The LIFE Study. *Circulation* 2005;112 (suppl II):II-459.
6. Kylin E. Studien über das hypertonie-hyperglykämie-hyperurikämiesyndrom. *Zentral-blatt für Innere Medizin* 1923;44:105-127.

7. Nan H, Qiao Q, Söderberg S, Pitkäniemi J, Zimmet P, Shaw J, Alberti G, Uusitalo U, Pauvaday V, Chitson P, Tuomilehto J. Serum uric acid and incident diabetes in Mauritian Indian and Creole populations. *Diabetes Res Clin Pract* 2008;80:321-327.
8. Denghan A, van Hoek M, Sijbrands EJG, Hofman A, Witteman JCM. High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. *Diabetes Care* 2008;31:361-362.
9. Dai CY, Chuang WL, Ho CK, Ou TT, Huang JF, Hsieh MY, Yu ML. High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. *Diabetes Care* 2008;31:e67.
10. Lippi G, Targher G, Montagnana M, Salvagno GL, Guidi GC. High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. *Diabetes Care* 2008;31:e68.
11. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Lindholm LH, Dahlöf B. In-Treatment Resolution or Absence of Electrocardiographic Left Ventricular Hypertrophy is Associated With Decreased Incidence of New-Onset Diabetes Mellitus in Hypertensive Patients. *Hypertension* 2007;50:984-990.
12. Dahlöf B, Devereux R, de Faire U, Fyhrquist F, Hedner T, Ibsen H, Julius S, Kjeldsen S, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: rationale, design, and methods. The LIFE Study Group. *Am J Hypertens* 1997;10(7 Pt 1):705–713.
13. Dahlöf B, Devereux RB, Julius S, Kjeldsen SE, Beevers G, de Faire U, Fyhrquist F, Hedner T, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Characteristics of 9194 patients with left ventricular hypertrophy: the LIFE study. Losartan Intervention For Endpoint Reduction in Hypertension. *Hypertension* 1998;32:989–997.
14. Boon NA, Colledge NR, Walker BR, Hunter JAA editors. *Davidson's Principles & Practice of Medicine*. 20th edition, 2006, p 1320.

15. Choi HK, Ford ES. Prevalence of the Metabolic Syndrome in Individuals with Hyperuricemia. *Am J Med* 2007;120:442-447.
16. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsyka K, Saito A, Sone H. Association Between Serum Uric Acid and Development of Type 2 Diabetes *Diabetes Care* 2009 ;32(9) :1737-1742.
17. Ioachimescu AG, Brennan DM, Hoar BM, Kashyap SR, Hoogwerf BJ. Serum uric acid, mortality and glucose control in patients with Type 2 diabetes mellitus : a PreCIS database study. *Diabetic Medicine* 2007;24:1369-1374.

Figure legends:

Figure 1. Incidence of New-Onset Diabetes (n = 522) According to Baseline Quartiles of Serum Uric Acid. $P < 0.001$ for trend (Chi-Square)

Figure 2. The highest versus the three lowest quartiles of SUA and risk of new-onset diabetes at baseline and at years 1 - 4. $P < 0.05$ (Cox regression analyses)

Footnotes to Figure 2

*Non-Significant.

Main Multivariate Model: Adjusted for treatment, baseline serum glucose, urinary albumin/creatinine ratio, eGFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage.

Table 1. Baseline Demographic and Clinical Characteristics of Patients without Diabetes at Baseline by Quartiles of Baseline SUA (n = 7489).

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P
	n=1884	n=1896	n=1829	n=1880	Value
Range (mg/dl)	1.16-4.62	4.64-5.48	5.49-6.33	6.35-11.93	
Serum uric acid (mg/dl)	4.0 ±0.6	5.1 ±0.2	5.9 ±0.2	7.3 ±0.8	< 0.001
Age (years)	67.4 ±7.0	67.2 ±7.0	66.7 ±6.9	66.2 ±7.0	< 0.001
Women	1506 (80%)	1173 (62%)	848 (46%)	525 (28%)	< 0.001
Black race	56 (3%)	70 (4%)	89 (5%)	162 (9%)	< 0.001
Weight (kg)	71.0 ±13.3	76.1 ±12.9	80.0 ±13.8	84.4 ±14.8	< 0.001
Height (cm)	164.0 ±8.3	166.7 ±9.2	168.4 ±9.5	171.0 ±9.1	< 0.001
BMI (kg/m^2)	26.4 ±4.4	27.4 ±4.4	28.2 ±4.7	28.9 ±4.6	< 0.001
Diastolic blood pressure (mmHg)	98 ±9	98 ±9	98 ±9	99 ±9	< 0.001
Pulse pressure (mmHg)	77 ±15	77 ±15	75 ±15	75 ±16	< 0.001
Alcohol (> 10 drinks/week)	38 (2.0%)	47 (2.5%)	78 (4.3%)	145 (7.7%)	< 0.001
Heart rate (beat/min)	74 ±11	73 ±11	73 ±11	73 ±11	0.02
Systolic blood pressure (mmHg)	175 ±14	174 ±14)	173 ±14	174 ±14	0.08
Sokolow-Lyon (mm)	30.0 ±9.8	30.0 ±10.4	30.2 ±10.6	30.6 ±10.7	0.20
Never exercise	403 (21%)	365 (19%)	377 (21%)	412 (22%)	0.20
Current smokers	310 (17 %)	317 (17%)	300 (16%)	331 (18%)	0.74
Cornell product (mm x ms)	2830.1 ±1077.0	2824.7 ±1057.8	2796.8 ±1023.9	2811.2 ±1029.4	0.77
Laboratory values					
Hemoglobin (g/dl)	13.8 ±1.1	14.1 ±1.1	14.4 ±1.2	14.6 ±1.3	< 0.001
Serum sodium (mEq/l)	140.1 ±2.7	140.3 ±2.4	140.5 ±2.5	140.7 ±2.4	< 0.001
Serum potassium (mEq/l)	4.1 ±0.4	4.2 ±0.4	4.2 ±0.4	4.2 ±0.4	< 0.001
Serum creatinine (mg/dl)	0.8 ±1.7	0.9 ±0.2	1.0 ±0.2	1.1 ±2.5	< 0.001
Estimated GFR (ml/min)	72.5 ±14.2	69.7 ±13.8	68.5 ±14.6	65.0 ±15.5	< 0.001
Urinary albumin/creat. ratio (mg/g)	31.6 ±106.2	46.5 ±340.2	51.2 ±174.0	80.4 ±280.1	< 0.001
Serum total cholesterol (mg/dl)	239.8 ±42.5	235.9 ±42.5	235.9 ±42.5	232.0 ±42.5	< 0.001

Serum HDL cholesterol (mg/dl)	65.7 ±19.3	61.9 ±15.5	58.0 ±15.5	54.1 ±15.5	< 0.001
Serum glucose (mg/dl)	95.5 ±18.0	97.3 ±18.0	99.1 ±18.0	102.7 ±19.8	< 0.001
Medical history					
Coronary heart disease	214 (11%)	267 (14%)	299 (16%)	326 (17%)	< 0.001
Congestive heart failure	12 (0.6%)	22 (1%)	33 (2%)	45 (2%)	< 0.001
Framingham risk score	16.8 ±7.2	19.9 ±8.4	22.6 ±9.0	25.4 ±9.1	< 0.001
Stroke	63 (3%)	63 (3%)	68 (4%)	95 (5%)	0.02
TIA	61 (3%)	61 (3%)	71 (4%)	88 (5%)	0.06
Isolated systolic hypertension	282 (15%)	273 (14%)	251 (14%)	228 (12%)	0.07
Peripheral vascular disease	102 (5%)	88 (5%)	102 (6%)	118 (6%)	0.18
COPD	64 (3%)	73 (4%)	79 (4%)	86 (5%)	0.27

Values are either mean ± SD or number (%) of subjects.

BMI = body mass index. Sokolow-Lyon voltage = (SV1+ RV5-6) and Cornell voltage-duration product = (RAvL + SV3 + 6 mm for women) x QRS are criteria of LVH in electrocardiogram. GFR = glomerular filtration rate; estimated GFR is calculated by the MDRD formula (175 x [(s-creat/88.4)$^{-1.154}$] x age $^{-0.203}$ x gender constant (men: 1.00; women: 0.742). Framingham risk score = risk score based on gender, cholesterol, HDL cholesterol, smoking status, presence of diabetes and LVH, systolic blood pressure and BMI. TIA = transitory ischemic attack. COPD = chronic obstructive pulmonary disease.

Table 2. Cox Proportional Hazards Models Demonstrating the Association of Serum Uric Acid with New-onset Diabetes in Patients without Diabetes at Baseline (n = 7489).

Variable	Hazard Ratio (95% CI)	P Value
Baseline SUA, pr SD (1.3 mg/dl)		
Univariate	1.43 (1.32-1.55)	< 0.001
Treatment adjusted	1.43 (1.32-1.55)	< 0.001
Multivariate main model	1.29 (1.18-1.42)	< 0.001
Multivariate model[1]	1.30 (1.19-1.43)	< 0.001
Multivariate model[2]	1.24 (1.13-1.36)	< 0.001
Multivariate model[3]	1.20 (1.09-1.32)	< 0.001
Multivariate model[4]	1.16 (1.06-1.28)	0.002
Multivariate model[5]	1.17 (1.07-1.29)	0.001
Baseline Quartiles of SUA[6]		
Univariate	1.43 (1.32-1.55)	< 0.001
Treatment adjusted	1.43 (1.32-1.55)	< 0.001
Multivariate main model	1.28 (1.18-1.40)	< 0.001
Multivariate model[1]	1.28 (1.17-1.40)	< 0.001
Multivariate model[2]	1.23 (1.13-1.35)	< 0.001
Multivariate model[3]	1.20 (1.10-1.31)	< 0.001
Multivariate model[4]	1.17 (1.07-1.28)	0.001
Multivariate model[5]	1.17 (1.06-1.28)	0.001
Time-varying SUA, pr SD (1.3 mg/dl)		
Univariate	1.22 (1.14-1.30)	< 0.001
Treatment adjusted	1.20 (1.12-1.28)	< 0.001
Multivariate main model	1.10 (1.02-1.19)	0.015

Multivariate model[1]	1.07 (1.00-1.16)	0.066
Multivariate model[2]	1.08 (1.00-1.17)	0.056
Multivariate model[3]	1.04 (0.96-1.12)	0.37
Multivariate model[4]	1.03 (0.95-1.11)	0.50
Multivariate model[5]	1.00 (0.92-1.08)	0.98

Multivariate main model: Adjusted for treatment with losartan vs. atenolol, baseline serum glucose, urinary albumin/creatinine ratio, estimated GFR and Framingham risk score, time-varying systolic and diastolic blood pressure, and time-varying LVH by Cornell voltage-duration product and Sokolow-Lyon voltage.

[1] Main model also adjusted for maximum dose hydrochlorothiazide during study.

[2] Main model also adjusted for baseline HDL.

[3] Main model also adjusted for baseline BMI.

[4] Main model also adjusted for baseline BMI and HDL.

[5] Main model also adjusted for baseline BMI, HDL and maximum dose hydrochlorothiazide during study.

[6] HR indicates the trend across the 4 SUA quartiles.

Supplemental Table. Univariate Predictors of New-onset Diabetes in Patients without Diabetes at Baseline (n = 7489).

Variable	Hazard Ratio (95% CI)	P Value
Serum uric acid (per SD [1.3 mg/dl])	1.43 (1.32-1.55)	< 0.001
Time-varying SUA (per SD [1.3 mg/dl])	1.22 (1.14-1.30)	< 0.001
Body Mass Index (per 1 kg/m^2)	1.09 (1.08-1.10)	< 0.001
Baseline Cornell (per 1 mm x ms)	1.00 (1.00-1.00)	< 0.001
Creatinine (per 0.01 mg/dl)	1.01 (1.00-1.01)	< 0.001
Estimated GFR (per 1 ml/min)	0.99 (0.98-1.00)	< 0.001
Framingham risk score (per 1 % point)	1.03 (1.02-1.04)	< 0.001
Glucose (per 18 mg/dl)	1.72 (1.65-1.79)	< 0.001
HDL (per 38.7 mg/dl)	0.23 (0.18-0.29)	< 0.001
Heart rate (per 1 beat/min)	1.01 (1.01-1.02)	< 0.001
Hemoglobin (per 0.1 g/dl)	1.02 (1.01-1.03)	< 0.001
Pulse pressure (per 1 mmHg)	1.01 (1.01-1.02)	< 0.001
Systolic blood pressure (per 1 mmHg)	1.02 (1.01-1.02)	< 0.001
Total cholesterol (per 38.7 mg/dl)	0.86 (0.79-0.93)	< 0.001
Treatment (atenolol vs. losartan)	1.38 (1.16-1.64)	< 0.001
Weight (per 1 kg)	1.03 (1.03-1.04)	< 0.001
Hydrochlorothiazide, max dose during study	1.03 (1.02-1.04)	< 0.001
Time-varying Sokolow-Lyon (per 10.5 mm)	0.85 (0.78-0.94)	0.001
Time-varying DBP (per 1 mmHg)	0.99 (0.98-1.00)	0.003
Potassium (per 1 mEq/l)	0.72 (0.57-0.91)	0.006
Exercise (yes vs. no)	0.77 (0.63-0.94)	0.01

Sokolow-Lyon (per 1 mm)	0.99 (0.98-1.00)	0.019
Time-varying Cornell (per 1050 mm x ms)	1.09 (1.01-1.17)	0.02
Diastolic blood pressure (per 1 mmHg)	1.01 (1.00-1.02)	0.10
Height (per 1 cm)	1.01 (1.00-1.02)	0.21

Some of the values in this table are converted from SI units to mg/dl.

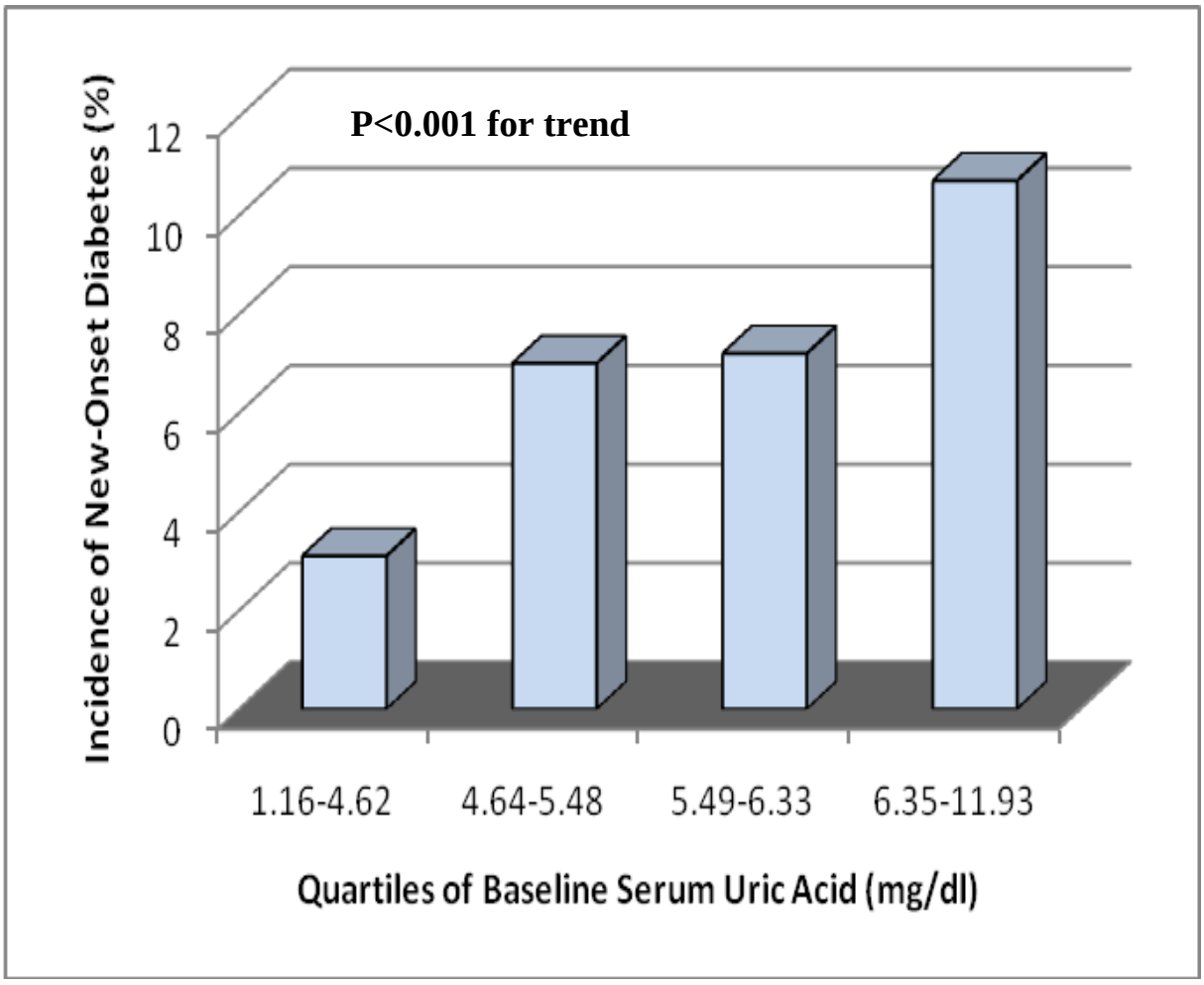
P<0.001 for trend
Incidence of New-Onset Diabetes (%)
0
2
4
6
8
10
12
1.16-4.62
4.64-5.48
5.49-6.33
6.35-11.93
Quartiles of Baseline Serum Uric Acid (mg/dl)

Fig. 1

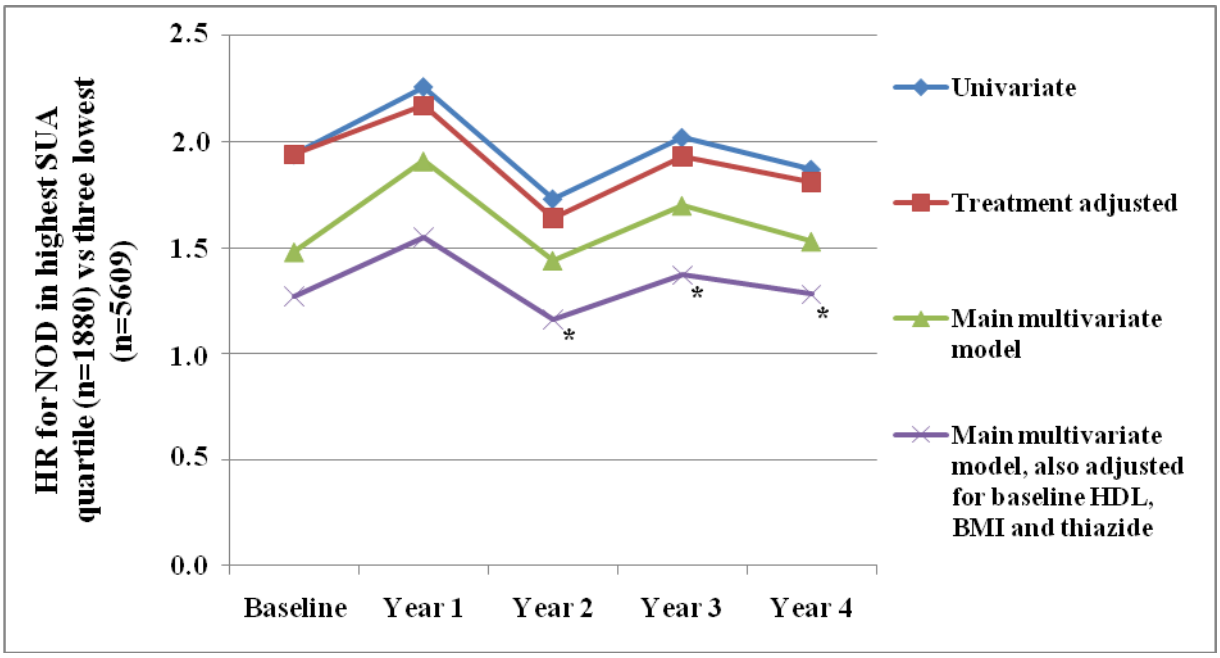
HR for NOD in highest SUA quartile (n=1880) vs three lowest (n=5609)
2.5
2.0
1.5
1.0
0.5
0.0
Baseline
Year 1
Year 2
Year 3
Year 4
*
*
*
Univariate
Treatment adjusted
Main multivariate model
Main multivariate model, also adjusted for baseline HDL, BMI and thiazide

Fig. 2